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SHORT COMMUNICATION

Polycystic ovary syndrome and epilepsy—a gynaecological perspective

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The prevalence of polycystic ovaries (PCO) and polycystic ovary syndrome (PCOS) in the general population is approximately 20 and 10%, respectively, and published studies suggest a similar prevalence in women with epilepsy. These data do not suggest that epilepsy is associated with a higher prevalence of the condition, and it would appear that the background prevalence of PCO and PCOS is the same as in the general population.

Key words: polycystic ovary syndrome; epilepsy; endocrine disorders; anti-epileptic drugs.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in the general population and as reproductive endocrine disorders are common in women with epilepsy, it is of no surprise that PCOS has been commonly observed in women with epilepsy. Women with epilepsy have significantly reduced fertility rates compared to the general population[1] and it has been shown that both epilepsy and its treatment can alter menstrual and fertility cycles[2]. When treating women of childbearing age with epilepsy, it is therefore important to consider the effect of the anti-epileptic drugs (AEDs) on reproductive health, as well as considering efficacy and tolerability.

Although several studies have proposed the possibility of a causal relationship between valproate and the increased occurrence of polycystic ovaries (PCO) and hyperandrogenism[3–5], these studies have been criticised for their retrospective design, and the findings contradicted by more recent studies. Due to the controversy in the area of epilepsy and PCOS, this review aims to outline current evidence linking epilepsy and AEDs to PCOS.

PCO

PCO are recognised with pelvic ultrasound as this provides a non-invasive method of assessing the morphological appearance of the ovary. They are characterised by the presence of multiple follicular cysts (10 or more), 2–8 mm in diameter, distributed either peripherally around a dense core of stroma or scattered throughout an increased amount of stroma[6]. PCO are generally enlarged and are initially recognised in puberty during the initiation of follicular activity at menarche[7]. Ultrasound evaluation has revealed the prevalence of PCO in the general female population to be approximately 20%[8–11], with a higher prevalence being observed in selected populations. They may not be associated with any hormonal or clinical abnormalities, but the most common feature is erratic or infrequent ovulation giving rise to menstrual irregularity. In a study of 173 women with anovulation or hirsutism, PCO has been identified in 26% of women with amenorrhoea, 87% of women with oligomenorrhoea and 92% of women with idiopathic hirsutism[6]. The typical features of PCO are shown in Table 1.

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Table 1: Typical features of polycystic ovaries.

Anatomical features	Clinical features	Endocrine features
Multiple (≥10) cysts measuring 2–8 mm in diameter	Menstrual abnormalities[a]	Normal levels of luteinizing hormone
Peripherally located but can be disseminated	Non-hirsute	Normal levels of testosterone
Enlarged ovary with increased ovarian stroma	Non-obese	

[a] 95% have an irregular menstrual cycle.

PCOS

PCOS is one of the most common reproductive endocrine disorders, with heterogeneous clinical and biochemical features, and is the most frequent cause of anovulation and hirsutism[7]. PCOS was first described by Stein and Leventhal in 1935, who presented a report of seven women with menstrual irregularity that had undergone laparotomy and bilateral ovarian wedge resection[13]. In this study, PCO were characterised histologically and found to be associated with amenorrhoea, obesity and hirsutism. Histological examination revealed the presence of bilateral sclerotic ovaries. Even in this early series of patients, the heterogeneity of clinical symptoms can be observed; although all patients had a history of irregular menses, only three women were obese and only four were hirsute.

Clinical symptoms of PCOS include obesity and/or hirsutism, which are seen in 40–50%[14, 15], and menstrual disorders, which are found in 30–70% of women with PCOS[9, 15]. Endocrine abnormalities associated with PCOS are multiple (Table 2), however, the most common findings include elevated luteinizing hormone levels, an increased luteinizing hormone/follicle stimulating hormone ratio and elevated serum androgen levels (free and total). Between 40 and 70% of women will have elevated luteinizing hormone or androgen concentrations[12, 16]. Women with PCOS also have lower sex hormone-binding globulin than normal[14], which leads to increased free testosterone levels. It is interesting to note, however, that ≥50% of women with PCO morphology have normal luteinizing hormone and testosterone levels[15] and that the clinical manifestation of androgen excess is not related to circulating androgen levels. It is possible for a woman with excessive hirsutism to have normal androgen concentrations, or conversely a woman with no clinical signs of hirsutism to have a raised serum androgen concentration.

Table 2: Typical features of polycystic ovary syndrome.

Clinical features	Endocrine features
Menstrual irregularity (oligomenorrhoea or amenorrhoea)	Increased luteinizing hormone concentrations
Subfertility	Increased luteinizing hormone/follicle stimulating hormone ratio
Obesity	Increased androgen production (testosterone, androstenedione)
Hirsutism and/or alopecia	Normal follicle stimulating hormone levels
Acne	Abnormal lipid profile
	Prolactin may be increased
	Insulin resistance producing hyperinsulinism

The heterogeneity in the signs and symptoms of PCOS has led to considerable controversy in this area due to the difficulty in establishing a uniformly accepted definition of PCOS. The absence of unifying diagnostic criteria has plagued research into this condition and many studies have been criticised for the variable methods used to establish the diagnosis. Many studies have defined PCOS using a limited number of features, such as finding clinical or endocrine abnormalities in isolation. In the UK, it is now generally accepted that PCO detected by ultrasound scan, in association with other clinical features (obesity, hirsutism, menstrual irregularities or endocrine abnormalities) provides a sound diagnostic criterion[15]. The prevalence of PCOS has been estimated to be 4%[17]. This study defined PCOS as ovulatory dysfunction, clinical evidence of hyperandrogenism and/or hyperandrogenaemia and the exclusion of related disorders, such as hyperprolactinaemia, thyroid disorders and non-classic adrenal hyperplasia. This definition is similar to the current UK definition as it excludes the isolated finding of PCO.

There is a clear distinction between PCO and PCOS; the morphologic appearance of PCO can exist without any clinical signs of the syndrome. In fact, PCO can be identified in girls as young as 6 months and are not part of a disease[7]. Although the ovarian volume can be reduced with the combined contraceptive pill, the classic morphological features of PCO can still be observed with an increased ovarian stroma and increased numbers of follicular cysts.

The pathogenesis of PCOS is uncertain and it is unlikely that a single mechanism could be applied to all cases of PCOS. Evidence suggests that abnormalities in the hypothalamic–pituitary–gonadal axis, hyperinsulinaemia, or local factors within the ovary, could all play a role and environmental factors, such as weight gain, may also induce the clinical expression of PCOS. Additionally, there is strong evidence for a genetic

basis for PCOS; PCO or clinical symptoms of PCOS are present in 31–87% of first-degree relatives of patients with fully developed PCOS[18]. The exact mechanism of inheritance remains unclear[19].

Under normal conditions the hypothalamic–pituitary–gonadal axis controls the synthesis and concentrations of sex hormones, however, abnormalities in the secretion of ovarian steroid and non-steroidal hormones seem to affect feedback from the PCO to both the pituitary and hypothalamus[20]. The disturbance of this mechanism in women with PCOS results in the formation of multiple small cysts.

PCOS is often associated with insulin resistance and consequently hyperinsulinaemia, and although both lean and obese women with PCOS show evidence of decreased insulin sensitivity, insulin resistance is most marked in the obese[12]. By suppressing the synthesis of sex hormone-binding globulin, insulin increases free androgen concentrations, subsequently increasing the degree of hirsutism. The positive correlation between insulin resistance and obesity means that in some women with PCO, the clinical manifestation of menstrual irregularity and hirsutism will only become apparent if there is an increase in weight and associated metabolic changes.

There is a close association between weight gain and an increase in anovulatory cycles and menstrual irregularity[21]. The clinical expression of PCO can be altered by ovarian suppression and changes in weight, with weight loss being recommended as the first-line therapeutic option for all women with obesity and PCOS.

Epilepsy and PCOS

Women with epilepsy may be exposed to hormonal imbalances that predispose them to the development of PCOS. Reproductive endocrine disorders, such as PCOS, are common in women with epilepsy[22], however, there is uncertainty as to whether it is epilepsy or its treatment that predisposes to PCOS. Both epilepsy and AEDs can have an effect on the feedback loop of the hypothalamic–pituitary–gonadal axis, which controls the synthesis and concentrations of sex hormones[23].

Some authors have suggested that epilepsy itself may induce PCOS. Herzog *et al.*[24] evaluated 50 women with partial seizures of the temporal lobe for reproductive dysfunction. Of these women, 56% had menstrual problems: 16% had amenorrhoea, 20% had oligomenorrhoea and 20% had an abnormal menstrual cycle interval. Of the women with menstrual dysfunction, 68% had reproductive endocrine disorders, 20% of the total were diagnosed with PCOS. Although these results confirm that reproductive dysfunction is unusually common among women with temporal lobe epilepsy, and suggest a possible association with endocrine dysfunction, no significant relationship was found between the use of AEDs and the occurrence of menstrual disorders. In this study, PCOS and hypogonadotrophic hypogonadism occurred significantly more often in women with epilepsy than in the general female population. In another study, the same group found that there was a significant difference between the EEG laterality distributions associated with polycystic ovarian syndrome and those associated with hypogonadotrophic hypogonadism[25]. Patients with PCOS and untreated temporal lobe epilepsy had predominantly left-sided interictal epileptiform discharges in the EEG. This distribution differed significantly from that of women with epilepsy who had no reproductive endocrine disorders. The fact that PCOS appears to be more frequent with left- than with right-sided unilateral temporal lobe epileptogenic discharges would also suggest that epilepsy induces PCOS[26].

Bilo *et al.*[27] assessed the reproductive endocrine function in 10 untreated epileptic women with normal menstrual cycles and in 5 normal controls and found that the luteinizing hormone pulse frequency was significantly higher in epileptic women, with a consequent reduction of the luteinizing hormone interpulse interval. The authors suggest that epilepsy may interfere with the functional activity of the gonadotropin-releasing hormone pulse generator and hypothesise a possible relationship between luteinizing hormone hyperpulsatability of normally cycling epileptic females and reproductive endocrine disorders in epileptic women.

Reproductive endocrine disorders have also been reported in women with primary generalised epilepsy[28]. In this study of 20 women of childbearing age (17 of which were receiving AED therapy with valproate and/or phenobarbital), 5 patients (25%) were diagnosed with reproductive endocrine disorders, 3 with PCOS and 2 with hypothalamic ovarian failure. All five patients with reproductive endocrine disorders had long-standing menstrual irregularities.

AEDs and PCOS

Several studies have been conducted in order to determine the effects, if any, of AEDs on endocrine disorders. Scandinavian studies have suggested that there is a possible link between valproate and PCO[3–5], however, the impact of AEDs on endocrine disorders is debated. In the study conducted by Herzog *et al.*[24], 6 of the 10 women with PCOS were not receiving AEDs, making it unlikely that the occurrence of PCOS was related to the use of AEDs.

The first Scandinavian study conducted by Isojärvi *et al*.[3] aimed to determine the frequency and types of reproductive endocrine disorders in a large group of women with epilepsy and to analyse the effects of seizure type, seizure frequency and AED therapy on the occurrence of these disorders. In this retrospective study, 238 women with epilepsy (mean age 33 years, range 18–45 years) were assessed and compared to 51 healthy controls (mean age 35 years, range 22–45 years). Twenty-nine (12%) were treated with valproate, 120 (50%) with carbamazepine, 12 (5%) with valproate and carbamazepine, and 62 (26%) with other medications, the mean duration of therapy was 9 years (range, 0–31); 15 (6%) were untreated. Menstrual disturbances were found in 45% of women receiving valproate alone and 25% of those receiving valproate in combination with carbamazepine, compared to 19% of those receiving carbamazepine alone and 13% of those receiving other medications. PCO were found in 43% of women receiving valproate ($n = 12$), 22% of women receiving carbamazepine ($n = 33$), 50% of women receiving valproate and carbamazepine ($n = 6$), 11% of women receiving other medications ($n = 7$) and in 5% of the normal control group.

Although the results of this study suggest a link between valproate therapy and PCOS, the study design had several weaknesses. A major criticism is that the retrospective nature of the study may have resulted in selection bias: a significant selection among patients treated with valproate is most probable, as the prevalence of valproate monotherapy (12%) is far below the expected prevalence of patients with idiopathic generalised epilepsy, who are likely to be aggravated by CBZ treatment[28]. Additionally, the study never distinguished clearly between PCO and PCOS. By describing the number of patients with PCO or elevated serum testosterone concentrations, an increase in PCOS was implied, but not actually demonstrated. Also, pre-treatment data were not available and the prevalence of PCO and menstrual disturbances was very low in the control group.

The results of Isojärvi *et al*. have been widely publicised. However, they are not supported by the results of two recent studies[22, 29]. Bauer *et al*.[22] conducted a prospective study in 93 women with partial epilepsy in order to determine whether PCOS is a common finding in women treated with AEDs. In this study the incidence of PCOS in patients treated with valproate monotherapy (11.1%) was similar to that for patients treated with carbamazepine (10%) and also to that in patients receiving no medication (10.5%). This suggests that the manifestation of PCOS in women with focal epilepsy is not related to the administration of either valproate or carbamazepine[22]. In another study investigating the effects of valproate, phenobarbital and carbamazepine on sex hormones and luteal function, Murialdo *et al*.[29] found that the prevalence of PCO did not differ significantly between treatment groups. In a similar study, the same group investigated menstrual cycle and ovarian appearance in women with epilepsy receiving anti-epileptic therapy[30]. Eighty-three out of 101 women (36 with idiopathic generalised epilepsy and 65 with partial epilepsy) treated with various AEDs had abdominal ultrasound. PCO were found in 16.9% of patients (21.0% with idiopathic generalised epilepsy and 14.5% with partial epilepsy). These prevalences are the same as reported in the general population[8–11].

In a smaller, more recent study Isojärvi *et al*.[4] evaluated the association of obesity and hyperinsulinaemia with valproate-related PCO and hyperandrogenism in women with epilepsy. The authors found that obesity was encountered in more than half of women receiving valproate, and proposed that weight gain is progressive and associated with low serum insulin-like growth factor-binding protein 1 (IGFBP-1) levels, which may lead to hyperandrogenism and PCO[4]. This study may also have been biased by its retrospective nature and it should be noted that the trial population was small, additionally the study never distinguished clearly between PCO and PCOS. Discontinuation of VPA therapy leads to a reversal of hyperinsulinaemia, hyperandrogenism, dyslipidaemia and PCO in 12 women followed prospectively for 1 year[5].

The theory that VPA induced weight gain leads to increased insulin resistance with consequent hyperinsulinaemia and finally PCOS does not explain why PCO and/or hyperandrogenism was also high in lean VPA-treated patients. In an editorial comment on this study, Herzog[26] proposed that epilepsy may induce PCOS and that PCOS is treated by enzyme-inducing AEDs, but not by valproate, which is an enzyme-inhibiting AED. By inducing hepatic enzymes that reduce biologically active testosterone in the serum and by increasing the binding and metabolism of testosterone, some AEDs may inadvertently treat hyperandrogenism and thus PCOS, while valproate therapy may not. SHBG is uniformly elevated by chronic treatment with phenytoin, carbamazepine, primidone and phenobarbitone, but not with valproate[31].

Additionally, in a pilot study conducted in 22 women with bipolar disorder, PCO-like changes were not observed in women receiving divalproex (valproate) or lithium[32]. Although this study was limited by small patient numbers and by a cross-sectional design, the results highlight the uncertainty as to the link between valproate and PCO-like changes.

DISCUSSION

Whether AEDs promote the development of PCO or PCOS remains uncertain with conflicting evidence from the published literature. With such a lack of reliable and scientific data, it seems surprising that recent guidelines[2] have been published implying that some AEDs should be avoided in women with epilepsy. The evidence that was reviewed by these guidelines was of medium to low validity (class II or III) identifying the need for methodologically sound research[33]. Surely, prospective studies, including large numbers of epileptic women, are needed to establish whether any AED promotes the development of PCO and PCOS. One such study is currently underway in order to establish whether the link between valproate and PCOS alleged by Isojärvi *et al*. can be substantiated by a prospective, randomised controlled trial in AED-naïve patients[34, 35]. This study also aims to investigate the anthropomorphic, ultrasonographic and biochemical effects of lamotrigine and topiramate on women with newly diagnosed epilepsy. Additionally, a prospective study in pre-pubescent girls with epilepsy, with a 10–15 year follow-up, is needed in order to establish ovarian morphology changes during puberty and to determine whether PCO are more common in women with epilepsy. This study would need to use sound diagnostic techniques, including pelvic ultrasonography.

There are few data on the association between epilepsy and PCOS, and importantly no studies have been conducted which include pre-treatment pelvic ultrasound in order to assess the prevalence of PCO(S) before AED treatment. Although studies conducted in Scandinavia raise the issue of an association between valproate and PCO in women with epilepsy, these studies have been criticised. The studies were conducted in very small patient numbers of a selected population, were retrospective, and did not clearly distinguish between PCO morphology and PCOS. The results of these studies have also been contradicted by more recent findings.

Current evidence suggests that it is unlikely that any AED can produce PCO from otherwise normal ovaries and there are no data to contraindicate the use of any AED in women with epilepsy. Although valproate has been widely studied in this area, there is no evidence to suggest that valproate should not remain a first-line treatment option for women of childbearing age with epilepsy. Although it is possible that weight gain may alter the endocrine, biochemical and clinical features to produce the PCOS in women who already had PCO, there is no conclusive evidence to support this and the mechanisms are not fully understood. Further investigation is needed.

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